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REVIEW ARTICLE

Beyond self-monitored plasma glucose and HbA1c: the role of non-traditional glycaemic markers in gestational diabetes mellitus

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ABSTRACT

Strict glycaemic management is the cornerstone of metabolic control in gestational diabetes mellitus (GDM). Current monitoring standards involve self-monitoring plasma glucose (SMBG) and haemoglobin A1c (HbA1c). However, both have important limitations. SMBG only reflects instantaneous blood glucose and the inconvenience of self-collecting blood frequently results in poor compliance. HbA1c provides information on blood glucose levels from the previous 2 to 3 months and it is influenced by iron-deficient states, common during pregnancy. There is an urgent need for new shorter-term glycaemic markers, as glycated albumin, fructosamine or 1,5-anhydroglucitol. Glycated albumin seems especially interesting as it provides information on blood glucose levels over the foregoing 2–3 weeks and it is not influenced by iron deficiency or the dilutional anaemia of pregnancy. Fructosamine has a precise and inexpensive measurement and it is not affected by haemoglobin characteristics. This review further discusses the potential value of these non-traditional indicators of glycaemic control in patients with GDM, outlining their possible future applications.

KEYWORDS

Gestational diabetes mellitus; haemoglobin A1c; glycated albumin; fructosamine; 1,5-anhydroglucitol; biomarkers

Introduction

Gestational diabetes mellitus (GDM) is a condition in women who have glucose intolerance with onset or recognition during pregnancy (Metzger and Coustan 1998; American College of Obstetricians and Gynecologists (ACOG) 2013; American Diabetes Association 2015). It has been steadily increasing since the 1990s (National Institutes of Health 2013). This is partly due to changes in its diagnostic criteria, but mostly because of changes in its known risk factors, as an advanced maternal age, higher body mass index, and racial and ethnic demography (International Diabetes Federation 2015; NICE Guideline 2015). In 2015, the International Diabetes Federation estimated GDM to affect approximately one in 25 pregnancies worldwide (International Diabetes Federation 2015).

Women with GDM are at higher risk of gestational hypertension, preeclampsia, caesarean delivery, and its associated potential morbidities and, most importantly, of developing diabetes later in life (Yogev et al. 2004; Bellamy et al. 2009; American College of Obstetricians and Gynecologists (ACOG) 2013). Adverse neonatal effects include macrosomia, operative delivery, shoulder dystocia, birth trauma, respiratory distress syndrome, myocardial hypertrophy, hypoglycaemia, hypocalcaemia, polycythaemia and hyperbilirubinemia (Metzger et al. 2008; International Diabetes Federation 2015; American College of Obstetricians and Gynecologists (ACOG) 2013; NICE Guideline 2015). Long-term effects, diabetes mellitus and metabolic syndrome, have been actively discussed.

Most of these perinatal maternal–infant complications can be prevented by an early detection of abnormal maternal glucose tolerance and good glycaemic control during pregnancy (Evers et al. 2002; Lauenborg et al. 2003).

The lack of international uniformity in the approach to ascertainment, diagnosis and management of GDM has been a major hurdle (Table 1). Nevertheless, most authors agree that the aims in GDM include (1) prevention of short-term perinatal complications in mothers and foetuses/neonates; (2) prevention of long-term adverse health outcomes in both mothers and their offspring. To meet these goals, universal timely screening for GDM, strict glycaemic control during pregnancy and rescreening revaluation and follow-up during the puerperium are of great importance (Kitzmiller et al. 1996; Hiramatsu et al. 2012). The prospective Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study revealed a continuous relationship between mild maternal hyperglycaemia at 24–32 weeks and adverse perinatal outcomes, highlighting even more the importance of attaining excellent glycaemic control during pregnancy (Metzger et al. 2008). Plasma glucose measurement is of great importance, but it is actually not possible to measure in all patients and it has limitations. HbA1c is currently the most widely used indicator of glycaemic control in clinical practice. However, there is a growing interest in the serum biomarkers of hyperglycaemia, such

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Table 1. Screening and diagnosis guidelines from different associations.

Organisation	Who to screen	Method of screening	Screen threshold (mmol/L)	Diagnostic test	Diagnostic threshold (mmol/L)
IADPSG	All women	"One-step" 75 g OGTT	N/A	N/A	Fasting ≥5.1 1 h ≥10.0 2 h ≥8.5 ≥1 level must be met
IDF	All women	"One–step" 75 g OGTT	N/A	N/A	Fasting ≥5.1 1 h ≥10.0 2h ≥8.5 ≥1 level must be met
ADA	All women	"One-step" 75 g OGTT	N/A	N/A	Fasting ≥5.1 1 h ≥10.0 2h ≥8.5 ≥1 level must be met
CDA	All women	50 g GCT (preferred) Alternative: "one-step" 75 g OGTT	≥7.8	75g OGTT	(a) ≥11.1 on 50 g GCT (b) 75 g OGTT Fasting ≥5.3 1h ≥10.6 2 h ≥9.0 ≥1 level must be met
NICE	Women with risk factors	Risk factors[b]	N/A	75 g OGTT	Fasting ≥7.0 2 h ≥7.8 ≥1 level must be met
ACOG	All women	50 g GCT	135 or ≥7.8[a]	100 g OGTT	(a) Fasting ≥5.3 1 h ≥10.0 2 h ≥ 8.6 3 h ≥ 7.8 or[a] (b) Fasting ≥5.8 1 h ≥10.6 2 h ≥ 9.2 3 h ≥ 8.0 ≥2 levels must be met
WHO	(a) Women with risk factors (b) All women	(a) Risk factors[c] (b) "One-step" 75g OGTT	N/A	75g OGTT	Fasting ≥7.0 2 h ≥7.8 ≥1 level must be met

ACOG: American College of Obtetricians and Gynecologists; ADA: American Diabetes Association; CDA: Canadian Diabetes Association; GCT: Glucose challenge test; IADPSG: International Association of Diabetes and Pregnancy Study Group; IDF: International Diabetes Federation; NICE: National Institute for Health and Care Excellence; OGTT: Glucose tolerance test; WHO: World Health Organisation.

[a]It is suggested that practitioners and institutions should select a single set of screening and diagnostic criteria for consistent use within their patient populations.

[b]Previous baby weighting ≥4.5 kg, previous GDM, first-degree relative with diabetes, family origin with a high prevalence of diabetes, body mass index >30 kg/m^2.

[c]Older women, obese women, previous history of glucose intolerance, history of GDM, pregnant women with elevated fasting or casual blood glucose levels, previous macrosomic baby, strong family history of diabetes, women from high-risk ethnic groups.

as fructosamine, glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG). Here, we will try to uncover their potential advantages and limitations in the management of GDM (Table 2).

Indicators of glycaemic control

The gold of glycaemic control during pregnancy is to bring plasma glucose level as close to normal as possible without the development of hypoglycaemia. The current monitoring standard for GDM involves self-monitoring of plasma glucose (SMBG). Continuous glucose monitoring is able to improve glycaemic control during the third trimester of pregnancy, and to decrease the risk of macrosomia (Murphy et al. 2008) in pregnant women with pregestational type 1 diabetes, but its potential use in GDM awaits further data and cost-effectiveness analysis. It has a high cost and needs to be performed by a healthcare professional.

SMBG enables strict glycaemic control. It also allows patients to understand the relationship between meals, snacks, events, activity and blood glucose levels. When insulin therapy is needed, its adjustments according to SMBG have demonstrated value in decreasing macrosomia, neonatal hypoglycaemia and caesarean section (Langer et al. 1989, 1991; De Veciana et al. 1995). However, it only reflects instantaneous blood glucose, which is susceptible to factors such as emotion or diet and provides no assessment on chronic or mean glycaemic levels. Furthermore, the pain and inconvenience of collecting blood from a finger (in most settings six times daily), frequently result in poor compliance.

Therefore, SMBG is an important part of current management of GDM but has limitations and does not substitute the information given by indicators of glycaemic control.

Haemoglobin A1c (HbA1c)

Amongst the glycated proteins known to be of interest in diabetes, Hb A1c was identified more than 40 years ago. It is currently in wide use as the standard marker for clinical management of diabetes. Besides its diagnostic value, it provides a reliable assessment of chronic glycaemic levels that are intimately related to the risk of diabetic complications. In red blood cells, HbA1c is haemoglobin that has glucose attached to the N-terminal valine of the beta chain, and is reported as a proportion of total haemoglobin. Because the lifespan of red blood cells is approximately 120 days, HbA1c, therefore, reflects average glycaemia over the past 1–4 months – Tahara

Table 2. Markers of glycaemic control in GDM.

Marker	Brief description	Duration of glycaemia reflected	Strengths	Limitations
HbA1c	Proportion of haemoglobin that is glycated	1–4 months	Low within-person variability; extensive experience in pregestational diabetes; readily available in most settings	Affected by alterations in red cell turnover; inaccurate results in the presence of certain haemoglobin variants with some methods of measurement; affected by iron deficiency states with and without anaemia in pregnant women with diabetes (pregestational and GDM); limited evidence linking to outcomes in GDM
Glycated albumin	Proportion of albumin that is glycated	2–3 weeks	Not affected by iron deficient states or iron deficiency anaemia (pregestational diabetes and GDM); not affected by dilutional anaemia of pregnancy	Influenced by conditions that interfere with albumin metabolism, as nephrotic syndrome or abnormal thyroid function; lacks widely accepted reference interval; limited evidence linking to outcomes; not available in many settings; method performance may vary
Fructosamine	Total serum protein glycation	2–4 weeks	Not affected by haemoglobin characteristics; not influenced by red cell turnover; measurement technically simple, rapid and precise; inexpensive	Affected by dilutional anaemia; influenced by conditions that interfere with albumin metabolism, as nephrotic syndrome or abnormal thyroid function; limited evidence linking to outcomes
1.5-Anhydroglucitrol	Monosaccharide filtered by the kidney and normally reabsorbed, when glycaemia exceeds the renal threshold (± 180 mg/dL), glucose competes with 1.5 AG for reabsortion, 1.5 AG is excreted in the urine, so serum levels drop	2–14 d	Tests readily available	Affected by the changes in renal threshold for glucose induced by pregnancy; limited evidence linking to outcomes

and Shima (1995) reported that 50% reflect plasma glucose level during the past 1 month, 25% reflect plasma glucose level during the past 1–2 months, and another 25% reflect plasma glucose level during the past 2–4 months. In addition, as pregnancy progresses, insulin resistance rapidly increases and glucose tolerance changes. So, during pregnancy, a marker that reflects glycaemic control status mostly in the previous 2–3 months may become of limited value.

The correlation of HbA1c with microvascular and macrovascular complications of diabetes is well known. However, pregnant women are usually excluded from these clinical studies, and chronic diabetic complications usually do not develop within a period as short as the few months of GDM.

It has been reported that in non-diabetic pregnant women the time course of HbA1c is characterised by a biphasic change with the trough level occurring at week 24 of pregnancy: HbA1c tends to decrease during the middle stage and increase during the end stage of pregnancy (Phelps et al. 1983; Worth et al. 1985; Hiramatsu et al. 2012). In a study conducted by Nielsen et al. (2004), however, HbA1c levels began to decline from early pregnancy and further decreased in late pregnancy. These changes are likely a mix between several sources of interference related with pregnancy.

Disadvantages of HbA1c include limited interpretability in the setting of abnormal erythrocyte altered lifespan (Panzer et al. 1982). In patients with iron deficiency anaemia, HbA1c is known to be elevated and it has already been demonstrated that HbA1c levels are also elevated in iron deficiency states without anaemia (Koga et al. 2007). When investigating the effect of iron deficiency on HbA1c in 47 non-diabetic Japanese pregnant women, the group of Hashimoto (2008) found that in normal pregnant women, iron deficiency progresses during the end stage of pregnancy and that there is a significant negative correlation between HbA1c and serum ferritin, transferring saturation and mean corpuscular haemoglobin. Therefore, in non-diabetic pregnant women, at the end-stage of pregnancy, as iron deficiency progresses, HbA1c increases. It is not known if iron supplementation during pregnancy is able to neutralise this phenomenon. Hashimoto et al. (2010) further conducted a longitudinal study in 17 pregnant Japanese women with diabetes (six with GDM) and found that HbA1c levels are also higher relative to plasma glucose level during the end stage of diabetic pregnancies, during which most women are iron deficient. Other factors that can modify HbA1c independent of the true level of glycaemia, studied outside the context of pregnancy, comprise cigarette smoking, consumption of alcohol and dietary fat, advanced kidney and liver disease, age and ethnic origin (Cohen and Herman 2014). In a very recent multicentre study aimed to identify the determinants of HbA1c in subjects with impaired glucose tolerance (Sakane et al. 2017), BMI was correlated with higher HbA1c in a multiple regression analysis. In pregnancy, few data exists, and to our knowledge, none in women with GDM. Nonetheless, in the study conducted by the Japan GA Study Group involving 574 healthy Japanese pregnant women that analysed GA and HbA1c influencing factors during pregnancy, HbA1 levels were higher in the obese group ($18.5 \leq$ BMI $< 25\ kg/m^2$) than those in of the control group (Hiramatsu et al. 2012).

Glycated albumin (GA)

GA is a ketoamine formed from a non-enzymatic reaction and binding between four lysine residues of albumin and glucose. It is an amadori compound, as is HbA1c, but albumin is reported to be approximately 10 times more sensitive to glycation than haemoglobin (Arasteh et al. 2014). Because the half-life of albumin is about 14 days, GA measurements are representatives of a far shorter period of exposure to circulating glucose than HbA1c, about 2–3 weeks (Koga and Kasayama 2010). Thus, GA is a better index of short-term glycaemic control than HbA1c. This may be of great interest in GDM, as metabolic alterations are far more dynamic than the prior 2–3 months assessed by HbA1c. Previous studies have shown that this glycaemic marker has a higher sensitivity to glycaemic fluctuations than HbA1c, and provides useful information in evaluating blood glucose in diabetic patients (Abe et al. 1993; Koga et al. 2006; Yoshiuchi et al. 2008). A study by Pan et al. (2013) which enrolled 713 pregnant women with abnormal 50 g GCT, showed that compared with HbA1c, GA is more closely correlated with fasting and postprandial glucose, regardless of insulin resistance and blood pressure, and so might be a better monitoring index in women with GDM. Furthermore, after being described that in premenopausal women, contrary to HgA1c, GA is not influenced by iron deficiency anaemia or iron deficiency state, the group of Hashimoto (2008) conducted a trial in 47 Japanese non-diabetic pregnant women that revealed once more, that in contrast to what happens with HbA1c during pregnancy, GA levels are not influenced by iron deficiency (Koga et al. 2007). The same group later reported the same phenomenon in pregnant women with diabetes (Hashimoto et al. 2010). GA levels are also unaffected by the dilutional anaemia of pregnancy (Hashimoto and Koga 2015). On the other hand, they can be influenced by conditions that interfere with albumin metabolism, as nephrotic syndrome or abnormal thyroid function (Okada et al. 2011; Koga et al. 2009). Research has also documented that BMI negatively influences GA levels. One study showed that GA levels decreased with increasing BMI in 2563 subjects with normal glucose tolerance (Wang et al. 2012). These findings were further confirmed in type 2 diabetes patients and obese children without diabetes (Koga et al. 2006; Nishimura et al. 2006). The underlying mechanism of the decreased GA levels and BMI elevations might be that obese individuals have a shorter-lived albumin and are in a state of chronic inflammation (Piva et al. 2013). A study involving 2118 pregnant women (639 with GDM and 1470 with normal glucose tolerance during pregnancy) that aimed to assess GA as a potential glycaemic index in managing GDM also showed that pre-pregnancy BMI was an important factor influencing GA levels throughout pregnancy (Li et al. 2015).

GA, as a new index of plasma glucose, lacks a widely recognised reference interval. In 2012, the Japan GA Study Group conducted a multicentre study involving 574 healthy Japanese pregnant women to determine the reference intervals of GA and HbA1c as glycaemic control markers. They also analysed their time courses and influencing factors during pregnancy. The reference intervals of GA and HbA1c throughout normal pregnancy were 11.5–15.7% and 4.5–5.7%, respectively. Furthermore, they noted that GA levels were decreased in obese pregnant women (BMI $\geq$25 Kg/m^2) and in those with proteinuria. Previously, the GA range proposed by Kohzuma et al. (2011) for the American population was 11.9–15.8% and the Shanghai Diabetes Institute in 2009 recommended that for the Chinese population, the GA range considered should be 11–17%. We have to admit the possibility of ethnic differences in GA, as described for HbA1c, but these ranges are quite similar (Selvin 2016).

Associations between indicators of glycaemic control and complications in the perinatal period have been explored. The GA Study Group of the Japanese Society of Diabetes and Pregnancy, considering the upper limits for HbA1c and GA (5.7% and 15.7%, respectively) in normal pregnant women previously mentioned, found that the incidences of neonatal hypoglycaemia, polycythaemia, respiratory disorder and large-for-gestational age foetuses was higher in the group of women with GA of more than 15.7%. On the other hand, it was reported that there was no significant increase in incidence in the group of women with HbA1c of more than 5.7%, compared with the group of women with HbA1c of 5.7% or less. Although a more accurate judgement should be made by ROC analysis for different cut-offs, in this case, GA was superior to HbA1c for prediction of perinatal complications (Shimizu et al. 2010). Sugawara et al. (2016) retrospectively studied 42 Japanese diabetic mothers (35 with GDM) and their offspring: mean GA and HbA1c were compared between mothers of infants with complications (25 cases) and those without complications (17 controls). GA differed significantly between the mothers of infants with versus without hypoglycaemia (15.5 ± 1.8 versus 13.8 ± 1.2%, $p = .001$), respiratory disorders (15.6 ± 1.8 versus 13.9 ± 1.2%, $p < .001$), hypocalcaemia (15.7 ± 2.1 versus 14 ± 1.2%, $p = .004$), myocardial hypertrophy (15.2 ± 1.9 versus 13.7 ± 1%, $p = .007$), and large-for-date status (15.8 ± 1.9 versus 14 ± 1.3%, $p = .002$). By contrast, HbA1c differed significantly between mothers of infants with respiratory disorders (6.4 ± 0.8 versus 5.7 ± 0.4%, $p = .002$), myocardial hypertrophy (6.2 ± 0.7 versus 5.7 ± 0.4%, $p = .009$), and large-for-date status (6.6 ± 0.8 versus 5.7 ± 0.4%, $p < .001$). As for hypoglycaemia (the most frequent complication of infants of diabetic mothers) and hypocalcaemia, HbA1c was not significantly different between the two groups. These results are consistent with the ones reported by Shimizu et al. (2010): from the point of view of infant complications, GA is useful for monitoring glycaemic control in pregnant women with diabetes. A case-control study conducted by Li et al. (2015), including 2118 Chinese pregnant women (639 with GDM and 1479 controls) found GA level $\geq$11.60% to be the best cut-off point for the poor glycaemic control in GDM—the area under the receiver operating characteristic curve for GA defining a good glycaemic control in GDM was 0.874 (95% confidence interval 0.811–0.938). Also, that the risk of birthweight $\geq$3500 g and macrosomia increased significantly with GA levels $\geq$13.00% and $\geq$12.00% at 36–38 weeks of gestation. Supported by this data, some authors now suggest the use of GA monitoring once/3–4 weeks as to reduce the frequency of SMBG, thereby increasing patients' compliance and lowering health care

costs (Hashimoto and Koga 2015). Others highlight the potential clinical utility of the combined information obtained from SMBG and a marker that accurately reflects variations in blood glucose levels and mean glycaemic status for short-term in GDM, as seems to be the case of GA (Li et al. 2015; Sugawara et al. 2016).

Fructosamine

Serum fructosamine results from the covalent attachment between a sugar (such as glucose or fructose) to total serum proteins, primarily albumin, therefore, forming ketoamines. It provides information on blood glucose levels over the foregoing 2–4 weeks, therefore, being a short-term marker (Ahmed and Furth 1992; Selvin et al. 2014). Fructosamine does not seem to be affected by haemoglobin characteristics. Nevertheless, and unlike HbA1c or GA, it is influenced by dilutional anaemia, which frequently develops during pregnancy. Because 60–70% of serum protein is albumin, conditions that affect the metabolism of the later, as nephritic syndrome or hyperthyroidism, can also interfere with fructosamine levels (Ford et al. 1987; Sako et al. 1989; Constanti et al. 1992). Its measurement is rapid, inexpensive, precise and technically simple. Even so, it is not routinely used in clinical practice. Nonetheless, fructosamine has been pointed out as a marker of exposure (the period of exposure and glucose variability) and a marker of risk (predictor of what will occur) in diabetes (Shafi et al. 2013; Parrinello and Selvin 2014; Ribeiro et al. 2016). It is currently used in populations where HbA1c is thought to inaccurately reflect glycaemia, including haemoglobinophaties and severe kidney disease (Shipman et al. 2014). Indeed, fructosamine and GA have been both cross-sectionally and prospectively associated with microvascular, macrovascular and all cause morbidity and mortality in dialysis patients, whereas many studies have reported no association of HbA1c with these outcomes (Kumeda et al. 2008; Yamada et al. 2008; Mittman et al. 2010; Murea et al. 2012).

As glucose tolerance may change very quickly during pregnancy, fructosamine may have an important role in the management of GDM. Parfitt et al. (1993) prospectively studied the relationships between fructosamine, HbA1c and mean blood glucose, determined from self-blood glucose monitoring, throughout 16 pregnancies in type 1 diabetic women. Fructosamine correlated best (Spearman rank) with mean blood glucose over the previous 2 weeks in the first and the second trimester (0.5) and over the previous week in the third trimester (0.39). HbA1c correlated best with mean blood glucose over the previous 8 weeks in the first and the second trimester (0.56), but over the previous 2 weeks in the third trimester (0.524). Also, from the Deming regression models, fructosamine predicted levels of mean blood glucose more precisely than HbA1. Authors concluded that an individual pregnant diabetic woman's mean blood glucose can be estimated from her level of fructosamine (more precisely) or HbA1c. Also that this can be useful to verify self-blood glucose monitoring data.

Few studies exist trying to evaluate associations between fructosamine levels and neonatal outcomes. A prospective cohort including 41 pregnant women with diabetes (27 with GDM) was carried out by Delgado et al. (2011), in which fructosamine, HbA1c and blood glucose were measured, as to evaluate the correlation between metabolic control and foetal macrosomia. No association was demonstrated. The correlation observed between fructosamine and fasting blood glucose ($r = 0.627$, $p < .001$) was superior to that of HbA1c and blood glucose ($r = 0.516$, $p < .001$). Another study conducted on 91 pregnant women with diabetes mellitus showed that second trimester plasma levels of fructosamine are related to the presence or absence of echocardiographic findings of congenital cardiopathies (Nogueira et al. 2010).

1,5-Anhydroglucitrol (1,5-AG)

1,5-AG is a monosaccharide obtained mainly from dietary resources that reflects average glycaemia over approximately the past 2–14 days. The relevance of 1,5-AG to diabetes stems from the fact that it normally almost all filtered 1,5-AG to be reabsorbed by the renal tubules. However, when glycaemia exceeds the renal threshold, at approximately 180 mg/dL, glucose competes with 1,5-AG for reabsorption by the renal tubule, and 1,5-AG is excreted in the urine, resulting in a drop in circulating 1,5-AG levels in the blood. As a result, the greater the extent and duration of the blood glucose above 180 mg/dL, the lower will be the 1,5-AG level in the blood (Buse et al. 2003; Dungan 2008; Yamanouchi and Akanuma 1994). Soybeans have particularly high levels of 1,5-AG, and certain foods such as rice, bread and beef contain modest levels; it is unclear as to what extent dietary intake may affect circulating 1,5-AG levels and the interpretation of this test (Buse et al. 2003). Because serum 1,5-AG is influenced by the threshold for urinary glucose excretion as well, serum 1,5-AG is low in renal glycosuria in which the threshold decreases. In dialysis or stage 4/5 kidney disease, the reabsorption of 1,5-AG decreases and, therefore, 1,5-AG levels are low. In other conditions, such as oxyhyperglycaemia, patients receiving long-term hyperalimentation, and liver cirrhosis, serum 1,5-AG is abnormally low (Emoto et al. 1992; Yamanouchi et al. 1995; Shimizu et al. 1999; Koga et al. 2011; Kim et al. 2012; Murai et al. 2014). Davison and Hytten (1975) reported that as during pregnancy the threshold for glucose in the kidney decreases, glycosuria may appear irrespective of glucose tolerance. Later, Tetsuo et al. (1990) showed that, because of this mechanism, 1,5-AG during pregnancy is low. Therefore, serum 1,5-AG does not seem to reflect glycaemic control accurately in pregnant women with diabetes.

Conclusion

HbA1c and self-monitored blood glucose have been the mainstay of metabolic control in GDM. However, both have important limitations. New markers of shorter-term glycaemia are urgently needed, to provide additional or substitute information to HbA1c, as metabolic alterations are far more dynamic than the 2–3 month prior period assessed by this measure and metabolic control is the cornerstone of good maternal and foetal outcomes.

GA is an attractive non-traditional marker of glycaemic control in pregnant women with diabetes: it provides accurate information from the previous 2–3 weeks, it is not influenced by iron deficient states common during pregnancy and it seems to be superior to HbA1c for prediction of some perinatal complications. However, it is not available in most clinical settings and still few clinical studies to date have assessed its validity in GDM management. Large-population epidemiological studies, representative of the various ethnic groups are needed. Fructosamine may also be an interesting marker in GDM and it has the advantage of having an inexpensive and technically simple measurement. However, contrary to GA, it is affected by dilutional anaemia, which is a physiologic adaptation during pregnancy and very little data exists on its association to clinical outcomes.

Randomised clinical trials may help establish construct validity and utility in one or more of this biomarkers and so help to determine if they can be an efficient and appropriate alternative to HbA1c in GDM. Moreover, a variety of possible future applications for these non-traditional biomarkers exists. As GDM is a heterogeneous condition, spanning from mild and occasional to a severe and persistent state of hyperglycaemia (resembling pregestational type 2 diabetes), some markers may reflect the severity of a woman's condition, or they may be more useful in a particular phase of these spectrum of dysglycaemic conditions of pregnancy. Also, in addition to assess glycaemic control and to help to predict some perinatal complications, glycaemic markers may even prove utility in the aid of treatment choices or add important information that can help us to foresee which women are more likely to become diabetic in the future. These are possibly some of the paths to the improvement of care in the field of hyperglycaemic disorders of pregnancy.

Disclosure statement

The authors report no declarations of interest.

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